

Radical Cation [4+2] Cycloaddition of Non-Conjugated Tetrasubstituted Alkenes by an FeCl₃/AgSbF₆ Co-Initiator

Shuhei Ohmura, Ryosuke Isogai, and Kazuaki Ishihara*^[a]

Dedication ((optional))

[a] Dr. S. Ohmura, R. Isogai, Prof. Dr. K. Ishihara
Graduate School of Engineering
Nagoya University
Furo-cho, Chikusa, Nagoya 464-8603 (Japan)
E-mail: ishihara@cc.nagoya-u.ac.jp

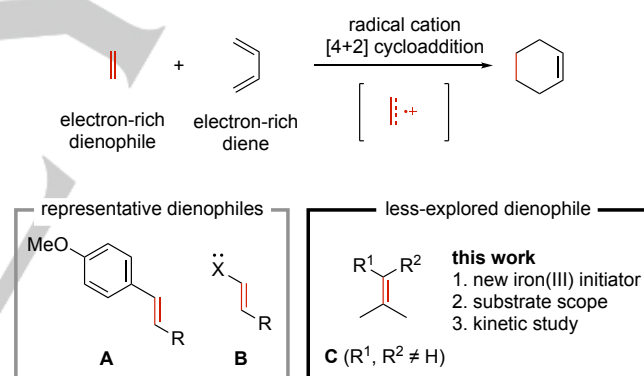
Supporting information for this article is given via a link at the end of the document. ((Please delete this text if not appropriate))

Abstract: Radical cation [4+2] cycloaddition is an alternative strategy for constructing various six-membered rings that cannot be easily accessed by thermal [4+2] cycloaddition. Here, we developed an FeCl₃/AgSbF₆ co-initiator to promote radical cation [4+2] cycloaddition of non-conjugated tetrasubstituted alkenes with 2,3-dimethyl-1,3-butadiene. In the presence of 10 mol% of FeCl₃ and 30 mol% of AgSbF₆, the reaction proceeded smoothly in MeCN to provide the cycloadducts from tetrasubstituted alkenes having an electron-rich aromatic group, which improved the yield. We demonstrate the efficiency of an FeCl₃/AgSbF₆ co-initiator by comparing our finding to the results with previously reported iron(III) initiators in an investigation of the substrate scope. In addition, a kinetic study was conducted to elucidate the detailed reaction mechanism, in which the rate-determining step can be facilitated by intramolecular single electron transfer.

The Diels–Alder reaction has been used extensively in organic synthesis due to its high reliability and efficiency for constructing versatile six-membered rings.¹ Essentially, the combination of an electron-deficient dienophile and an electron-rich diene is preferred to enhance the reaction rate. Use of the electrically reversed combination, the so-called inverse-electron-demand Diels–Alder reaction, is also effective.² As a complement to such conventional Diels–Alder reactions, radical cation [4+2] cycloaddition has received increased attention since it can combine both electron-rich reactants.³ Generally, the reaction is initiated by one-electron oxidation of an electron-rich dienophile to generate a radical cation intermediate which reacts with a diene (Scheme 1). Over the past few decades, a variety of strategies have been developed to generate the corresponding radical cation from electron-rich dienophiles such as anetholes⁴ (**A**) and heteroatom-substituted alkenes (**B**) including vinyl ethers,⁵ vinyl sulfides⁶ and enamines.⁷ Tetrasubstituted alkene (**C**) shows an oxidation potential comparable to those of the dienophiles,^{8,9} and is likely to be oxidized to generate a radical cation, but little is known about its application to radical cation [4+2] cycloaddition.¹⁰ Practical use of such readily accessible hydrocarbons for constructing valuable six-membered rings is synthetically attractive, and therefore further study is desirable.

From the viewpoint of environmental benefits, iron(III) salts have been widely used as one-electron oxidants to initiate both radical cation [4+2] and [2+2] cycloadditions of anetholes.¹¹ In

2018, Kang and Zhong developed an iron(III)–polypyridyl complex and Fe(ClO₄)₃, respectively.^{12,13} Recently, we found that cationic iron(III) salts (FeCl₃ and Fe(OTf)₃) could effectively oxidize both electron-deficient and electron-rich anetholes.¹⁴ Here, we report an FeCl₃/AgSbF₆ co-initiator for tetrasubstituted alkenes. To demonstrate its reactivity, the substrate scope was investigated, and our findings were compared to the results obtained by using previously reported iron(III) salt initiators.



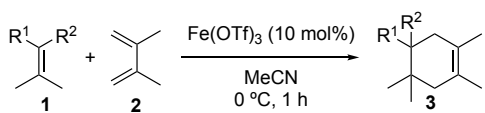
Scheme 1. Radical Cation [4+2] Cycloaddition.

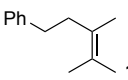
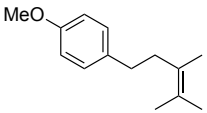
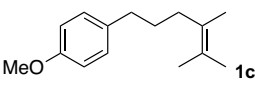
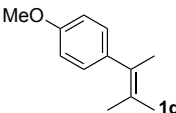
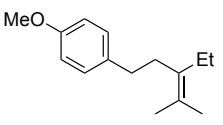
Based on our previous works,¹⁴ an initial study was conducted with the use of Fe(OTf)₃ as an initiator and reactions were carried out in MeCN at 0 °C (Table 1). When 10 mol% of Fe(OTf)₃ was used, [4+2] cycloaddition of alkene **1a** with 2,3-dimethyl-1,3-butadiene **2** proceeded, to afford the cycloadduct **3a** in 32% yield (entry 1). Encouraged by the works of Chiba, Kamiya, and Okada,^{10,15} we synthesized alkenes with a non-conjugated electron-rich aromatic group which facilitates radical cation cycloadditions by intramolecular single electron transfer (SET). As intended, substituting a phenyl group for a 4-methoxyphenyl group dramatically improved the yield (entry 2), while **1c** with a longer alkyl chain failed to work as well (entry 3). On the other hand, conjugated alkene **1d** was found to be inactive, presumably due to the steric hindrance (entry 4). Addition of 4-methoxybenzene to the reaction mixture of **1a** and **2** did not improve the yield, indicating that intermolecular SET was not operative (entry 5). Introducing an Et group negatively affected

COMMUNICATION

the reactivity, and the corresponding cycloadduct **3e** was obtained from **1e** in only 46% yield (entry 6).

Table 1. Initial Study.^[a]

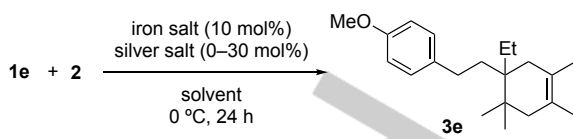


Entry	Dienophile	Yield of 3 [%] ^[b]
1	 1a	3a , 32
2	 1b	3b , 84
3	 1c	3c , 37
4	 1d	3d , 0
5 ^[c]	1a + 4-methoxybenzene	3a , 28
6	 1e	3e , 46

[a] Unless otherwise noted, the reaction was carried out using Fe(OTf)₃ (10 mol%), **1** (0.185 mmol) with **2** (0.555 mmol) in MeCN at 0 °C for 1 h. [b] The yield was determined by ¹H NMR analysis using 1,3-dinitrobenzene as an internal standard. [c] 4-Methoxybenzene (0.185 mmol) was added.

To improve the yield of **3e**, we screened several solvents (Table 2, entries 1–4). However, MeCN still gave better result, and less polar solvents were found to be not suitable in this reaction, probably because low polar solvents enhance the coordination of a counter anion to the radical cation intermediates, leading to the decreased reactivity. Next, we used cationic silver salts as an additive to cause chloride abstraction from FeCl₃ to generate reactive iron(III) species.¹⁶ After screening several silver salts, we found that AgSbF₆ shows high efficiency. As a result, the cycloadduct **3e** was obtained in 90% yield by using 10 mol% of FeCl₃ and 30 mol% of AgSbF₆ (entry 7). We confirmed that AgSbF₆ itself did not show any reactivity, suggesting that the generation of radical cation is caused by iron(III) species (entry 8). The preliminary experiment using 20 mol% of AgSbF₆ indicates that complete chloride abstraction is important for the reactivity (entry 9), and Fe(SbF₆)₃ might be generated from 1:3 ratio of FeCl₃ and AgSbF₆. Although further study is needed to detect the structure of active initiator,¹⁷ we reasoned that SbF₆⁻ acts as a non-coordinating counter anion of the radical cation intermediates to increase the efficiency of each reaction step.^{4f, 4s}

Table 2. Optimization of Conditions^[a]

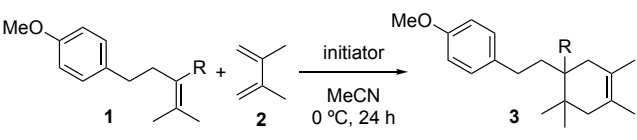


Entry	Iron salt	Silver salt	solvent	Yield of 3e [%] ^[b]
1	Fe(OTf) ₃	none	CH ₂ Cl ₂	0
2	Fe(OTf) ₃	none	Et ₂ O	<5
3	Fe(OTf) ₃	none	THF	<5
4	Fe(OTf) ₃	none	MeCN	49
5	FeCl ₃	AgNTf ₂ (30 mol%)	MeCN	51
6	FeCl ₃	AgBF ₄ (30 mol%)	MeCN	81
7	FeCl ₃	AgSbF ₆ (30 mol%)	MeCN	90
8	none	AgSbF ₆ (30 mol%)	MeCN	0
9	FeCl ₃	AgSbF ₆ (20 mol%)	MeCN	72

[a] Unless otherwise noted, the reaction was carried out using iron salt (10 mol%), silver salt (0–30 mol%), **1e** (0.185 mmol) with **2** (0.555 mmol) in MeCN at 0 °C for 24 h. [b] The yield was determined by ¹H NMR analysis using 1,3-dinitrobenzene as an internal standard.

Next, we performed comparative experiments using previously reported iron(III) salt initiators (Table 3). The corresponding cycloadduct **3b** was obtained in high yield from **1b** and **2** regardless of the kind of initiators. An FeCl₃/AgSbF₆ co-initiator was shown to have high efficiency by conducting the reaction using **1e** or **1f**, whereby the products were obtained in better yield than reactive initiator Fe(ClO₄)₃. However, **1g** was difficult to use in our system, even though greater amounts of initiators were loaded. Finally, **1h** with a sterically demanding *i*-Bu group completely stopped the reaction, and the starting material was just recovered.

Table 3. Evaluation of Iron(III) Salt Initiators and Substrate Scope.^[a]



Initiator [mol%]	Yield of 3 (R) [%] ^[b]				
	3b (Me)	3e (Et)	3f (Pr)	3g (CH ₂ CH ₂ Ph)	3h (<i>i</i> -Bu)
Fe(OTf) ₃ , 10	90	49	–	–	–
FeCl ₃ , 10	90	53	–	–	–
Fe(ClO ₄) ₃ , 10	95	77	63	–	–
FeCl ₃ , 10 / AgSbF ₆ , 30	99 ^[c]	90	71	32 (46 ^[d])	0

[a] Unless otherwise noted, the reaction was carried out using iron(III) salt (10 mol%), silver salt (0 or 30 mol%), **1** (0.185 mmol) with **2** (0.555 mmol) in MeCN at 0 °C for 24 h. [b] The yield was determined by ¹H NMR analysis using 1,3-dinitrobenzene as an internal standard. [c] Isolated yield. [d] FeCl₃ (20 mol%) and AgSbF₆ (60 mol%) were used.

To obtain insight into such a strong steric effect, we conducted a kinetic study to reveal the rate-determining step. In the following

experiments, we used $\text{Fe}(\text{ClO}_4)_3$ as an initiator instead of $\text{FeCl}_3/\text{AgSbF}_6$ because of the simple procedure to set up the reactions. In the presence of catalytic amounts of $\text{Fe}(\text{ClO}_4)_3$, the initial reaction rate of [4+2] cycloaddition of **1e** and **2** was measured (see the supporting information). As a result, zero-order dependency for both **1e** and **2** was observed, which suggested that neither the dienophile nor the diene is directly involved in the rate-determining step.

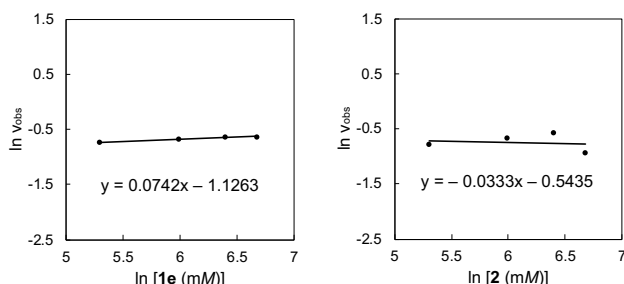


Figure 1. Kinetic study for **1e** and **2**. Standard reaction conditions: $\text{Fe}(\text{ClO}_4)_3$ (0.0010 mmol, 0.5 mol%), **1e** (0.20 mmol) and **2** (0.20 mmol) in MeCN (500 μL) at 0 $^\circ\text{C}$. Based on the standard conditions, **1e** (0.10–0.40 mmol) and **2** (0.10–0.40 mmol) were investigated, respectively.

Based on the results of the kinetic study and previous reports describing the effects of electron-rich aromatic groups connected to alkenes,¹⁵ we suggest the proposed mechanism in Figure 2. First, cationic iron(III) species oxidizes tetrasubstituted alkene **1** to generate radical cation intermediate **1^{•+}**. The 1st C–C bond formation between **1^{•+}** and **2** should occur regioselectively to avoid steric hindrance, forming distonic radical cation **4^{•+}**. We concluded that the rate-determining step is the subsequent 2nd C–C bond formation which overcomes the generation of a highly congested quaternary carbon center, accounting for the results of the kinetic study and the strong steric effect. We should note that the 2nd C–C bond formation in radical cation cycloaddition is generally considered to be very fast, since distonic radical cation species is highly reactive.¹⁸ Due to its steric hindrance around the double bond, however, tetrasubstituted alkene probably hampers this step, and therefore the facilitation by intramolecular SET was effective. Finally, reduction of **3^{•+}** by **1** provides **3** with regeneration of **1^{•+}** to complete the cycle.

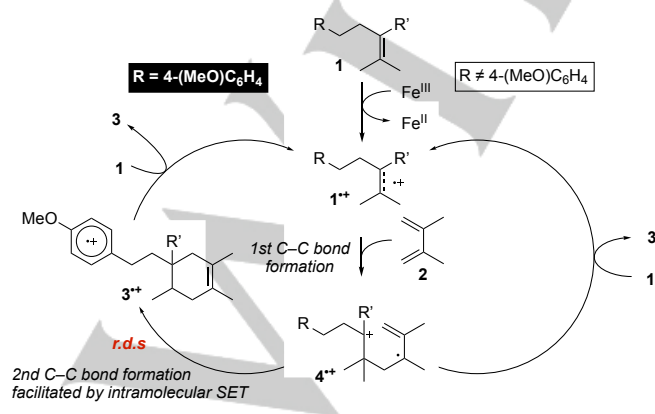


Figure 2. Proposed Mechanism.

In summary, we developed an $\text{FeCl}_3/\text{AgSbF}_6$ co-initiator for radical cation [4+2] cycloaddition of non-conjugated tetrasubstituted alkenes with 2,3-dimethyl-1,3-butadiene. Judicious choice of cationic silver salts as additives enabled us to promote the [4+2] cycloaddition of tetrasubstituted alkenes with a broader scope than previously reported iron(III) salt initiators. In addition, a kinetic study revealed the detailed reaction mechanism, in which an unusual rate-determining step could be facilitated by intramolecular SET.

Experimental Section

A test tube was charged with FeCl_3 (0.0185 mmol, 10 mol%) and AgSbF_6 (0.0555 mmol, 30 mol%) and MeCN (600 μL) under ambient conditions. After the mixture was stirred for 1 h at room temperature, diene **2** (0.555 mmol, 3 equiv) and dienophile **1** (0.185 mmol, 1 equiv) were added at 0 $^\circ\text{C}$. After stirring for 24 h, the reaction mixture was passed through a short pad of silica gel with AcOEt to quench the reaction, and the organic solvent was removed under reduced pressure to give the crude mixture.

Acknowledgements

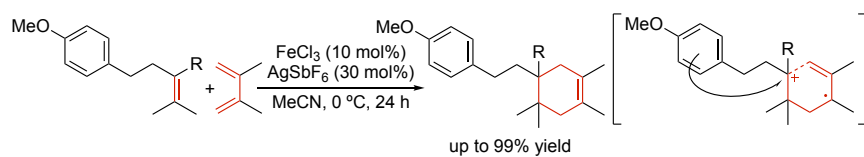
This work was financially supported by JSPS KAKENHI Grant Number JP15H05755 (to K.I.), the Grant Program of Innovation for Future Society (to K.I. and S.O.), and the JSPS Research Fellowship for Young Scientists Program (to S.O.).

Keywords: radical cation • [4+2] cycloaddition • iron(III) salt • silver salt • single electron transfer

- [1] a) H. B. Kagan, O. Riant, *Chem. Rev.* **1992**, *92*, 1007–1019; b) E. J. Corey, *Angew. Chem. Int. Ed.* **2002**, *41*, 1650–1667; c) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassiliou-giannakis, *Angew. Chem. Int. Ed.* **2002**, *41*, 1668–1698; d) J.-A. Funel, S. Abele, *Angew. Chem. Int. Ed.* **2013**, *52*, 3822–3863.
- [2] a) X. Jiang, R. Wang, *Chem. Rev.* **2013**, *113*, 5515–5546; b) J. Zhang, V. Shukla, D. L. Boger, *J. Org. Chem.* **2019**, *84*, 9397–9445.
- [3] a) N. L. Bauld, *Tetrahedron* **1989**, *45*, 5307–5363; b) N. J. Saettel, J. Oxgaard, O. Wiest, *Eur. J. Org. Chem.* **2001**, 1429–1439; c) Y. Okada, K. Chiba, *Chem. Rev.* **2018**, *118*, 4592–4630; d) T. Horibe, K. Ishihara, *Chem. Lett.* **2020**, *49*, 107–113.
- [4] a) D. W. Reynolds, N. L. Bauld, *Tetrahedron* **1986**, *42*, 6189–6194; b) W. Yueh, N. L. Bauld, *J. Phys. Org. Chem.* **1996**, *9*, 529–538; c) D. Gao, N. L. Bauld, *J. Org. Chem.* **2000**, *65*, 6276–6277; d) S. Lin, M. A. Ischay, C. G. Fry, T. P. Yoon, *J. Am. Chem. Soc.* **2011**, *133*, 19350–19353; e) S. S. Lin, C. E. Padilla, M. A. Ischay, T. P. Yoon, *Tetrahedron Lett.* **2012**, *53*, 3073–3076; f) E. P. Farney, S. J. Chapman, W. B. Swords, M. D. Torelli, R. J. Hamers, T. P. Yoon, *J. Am. Chem. Soc.* **2019**, *141*, 6385–6391; g) S. M. Stevenson, M. P. Shores, E. M. Ferreira, *Angew. Chem. Int. Ed.* **2015**, *54*, 6506–6510; h) R. F. Higgins, S. M. Fatur, S. G. Shepard, S. M. Stevenson, D. J. Boston, E. M. Ferreira, N. H. Damrauer, A. K. Rappé, M. P. Shores, *J. Am. Chem. Soc.* **2016**, *138*, 5451–5464; i) S. M. Stevenson, R. F. Higgins, M. P. Shores, E. M. Ferreira, *Chem. Sci.* **2017**, *8*, 654–660; j) R. F. Higgins, S. M. Fatur, N. H. Damrauer, E. M. Ferreira, A. K. Rappé, M. P. Shores, *ACS Catal.* **2018**, *8*, 9216–9225; k) Y. Zhao, M. Antonietti, *Angew. Chem. Int. Ed.* **2017**, *56*, 9336–9340; l) P. D. Morse, T. M. Nguyen, C. L. Cruz, D. A. Nicewicz, *Tetrahedron* **2018**, *74*, 3266–3272; m) K. Tanaka, M. Kishimoto, M. Sukekawa, Y. Hoshino, K. Honda, *Tetrahedron Lett.* **2018**, *59*, 3361–3364; n) J. Kollmann, Y. Zhang, W. Schilling, T. Zhang, D. Riemer, S. Das, *Green Chem.* **2019**, *21*, 1916–1920; o) S. L. Drew, A. L. Lawrence, M. S. Sherburn, *Chem. Sci.*

- 2015, 6, 3886–3890; p) Y. Okada, Y. Yamaguchi, A. Ozaki, K. Chiba, *Chem. Sci.* **2016**, 7, 6387–6393; q) A. Ozaki, Y. Yamaguchi, Y. Okada, K. Chiba, *ChemElectroChem* **2017**, 4, 1852–1855; r) Y. Imada, Y. Okada, K. Chiba, *Beilstein J. Org. Chem.* **2018**, 14, 642–647; s) N. Shida, Y. Imada, S. Nagahara, Y. Okada, K. Chiba, *Commun. Chem.* **2019**, 2, 24; t) K. Nakayama, N. Maeta, G. Horiguchi, H. Kamiya, Y. Okada, *Org. Lett.* **2019**, 21, 2246–2250; u) K. Nakayama, H. Kamiya, Y. Okada, **2020**, *J. Electrochem. Soc.* **167**, 155518; v) K. Liang, S. Wang, H. Cong, L. Lu, A. Lei, *CCS Chem.* **2021**, 3, 1727–1734.
- [5] a) J. Mattay, J. Gersdorf, J. Mertes, *J. Chem. Soc., Chem. Commun.*, **1985**, 1088–1090; b) D. W. Reynolds, K. T. Lorenz, H. S. Chiou, D. J. Bellville, R. A. Pabon, N. L. Bauld, *J. Am. Chem. Soc.* **1987**, 109, 4960–4968; c) N. L. Bauld, J. Yang, *Org. Lett.* **1999**, 1, 773–774; d) R. Shimizu, Y. Okada, K. Chiba, *Beilstein J. Org. Chem.* **2018**, 14, 704–708.
- [6] a) R. A. Pabon, D. J. Bellville, N. L. Bauld, *J. Am. Chem. Soc.* **1983**, 105, 5158–5159; b) B. Harirchian, N. L. Bauld, *Tetrahedron Lett.* **1987**, 28, 927–930; c) S. Lin, M. A. Ischay, C. G. Fry, T. P. Yoon, *Org. Lett.* **2017**, 19, 368–371.
- [7] a) N. L. Bauld, B. Harirchian, D. W. Reynolds, J. C. White, *J. Am. Chem. Soc.* **1988**, 110, 8111–8117; b) A. Gieseler, E. Steckhan, O. Wiest, *Synlett.* **1990**, 275–277; c) A. Gieseler, E. Steckhan, O. Wiest, F. Knoch, *J. Org. Chem.* **1991**, 56, 1405–1411; d) O. Wiest, E. Steckhan, *Tetrahedron Lett.* **1993**, 34, 6391–6394; e) T. Peglow, S. Blechert, E. Steckhan, *Chem. Commun.* **1999**, 433–434; f) U. Haberl, E. Steckhan, S. Blechert, O. Wiest, *Chem. Eur. J.* **1999**, 5, 2859–2865; g) S. P. Pitre, T. P. Yoon, J. C. Scaiano, *Chem. Commun.*, **2017**, 53, 4335–4388; h) S. P. Pitre, J. C. Scaiano, T. P. Yoon, *ACS Catal.* **2017**, 7, 6440–6444.
- [8] B.-J. Zhao, D. H. Evans, N. A. Macías-Ruvalcaba, H. J. Shine, *J. Org. Chem.* **2006**, 71, 3737–3742.
- [9] H. G. Roth, N. A. Romero, D. A. Nicewicz, *Synlett* **2016**, 27, 714–723.
- [10] A. Ozaki, Y. Yamaguchi, Y. Okada, K. Chiba, *Chin. J. Chem.* **2019**, 37, 561–564.
- [11] a) H. Ohara, T. Itoh, M. Nakamura, E. Nakamura, *Chem. Lett.* **2001**, 30, 624–625; b) T. Horibe, K. Katagiri, K. Ishihara, *Adv. Synth. Catal.* **2020**, 362, 960–963.
- [12] J. H. Shin, E. Y. Seong, H. J. Mun, Y. J. Jang, E. J. Kang, *Org. Lett.* **2018**, 20, 5872–5876.
- [13] Y. Yu, Y. Fu, F. Zhong, *Green Chem.* **2018**, 20, 1743–1747.
- [14] a) T. Horibe, S. Ohmura, K. Ishihara, *J. Am. Chem. Soc.* **2019**, 141, 1877–1881; b) T. Horibe, S. Ohmura, K. Ishihara, *Asian J. Org. Chem.* **2020**, 9, 395–398.
- [15] a) Y. Okada, N. Maeta, K. Nakayama, H. Kamiya, *J. Org. Chem.* **2018**, 83, 4948–4962; b) N. Maeta, H. Kamiya, Y. Okada, *Org. Lett.* **2019**, 21, 8519–8522; c) G. Horiguchi, H. Kamiya, Y. Okada, *J. Electrochem. Soc.* **2020**, 167, 155529.
- [16] H. Albright, H. L. Vonesh, C. S. Schindler, *Org. Lett.* **2020**, 22, 3155–3160.
- [17] We tried to conduct X-ray analysis to detect the structure of active initiator, but it was unsuccessful. When 1 equiv of FeCl₃ and 3 equiv of AgSbF₆ were stirred in MeCN, white precipitate was immediately generated, which we regarded as AgCl, and it was removed by filtration. After removing MeCN under reduced pressure, brown solid was obtained, but we could not crystallize it.
- [18] a) N. L. Bauld, R. Pabon, *J. Am. Chem. Soc.* **1983**, 105, 633–634; b) C. A. Marquez, H. Wang, F. Fabbretti, J. O. Metzger, *J. Am. Chem. Soc.* **2008**, 130, 17208–17209.

Entry for the Table of Contents



We developed a new reactive iron (III) initiator for radical cation [4+2] cycloaddition. In the presence of 10 mol% of FeCl₃ and 30 mol% of AgSbF₆, [4+2] cycloaddition of non-conjugated tetrasubstituted alkenes with 2,3-dimethyl-1,3-butadiene provided the cycloadduct in up to 99% yield. In addition, a kinetic study proposed that ring closure is the rate-determining step, which could be accelerated by intramolecular single electron transfer.

Institute and/or researcher Twitter usernames: @Plodide